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GAIL MUSEN, PHD[1]
ALAN M. JACOBSON, MD[1]
CHRISTOPHER M. RYAN, PHD[2]
PATRICIA A. CLEARY, MS[3]
BARBARA H. WABERSKI, MS[3]
KATIE WEINGER, EDD[1]
WILLIAM DAHMS, MD[4]†
MEG BAYLESS, RN[5]
NANCY SILVERS, RN[6]
JUDITH HARTH, RN[7]
NEIL WHITE, MD, CDE[8]
THE DIABETES CONTROL AND COMPLICATIONS TRIAL/EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (DCCT/EDIC) RESEARCH GROUP*

OBJECTIVE — The purpose of this study was to evaluate whether severe hypoglycemia or intensive therapy affects cognitive performance over time in a subgroup of patients who were aged 13–19 years at entry in the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS — This was a longitudinal study involving 249 patients with type 1 diabetes who were between 13 and 19 years old when they were randomly assigned in the DCCT. Scores on a comprehensive battery of cognitive tests obtained during the Epidemiology of Diabetes Interventions and Complications follow-up study, ~18 years later, were compared with baseline performance. We assessed the effects of the original DCCT treatment group assignment, mean A1C values, and frequency of severe hypoglycemic events on eight domains of cognition.

RESULTS — There were a total of 294 reported episodes of coma or seizure. Neither frequency of hypoglycemia nor previous treatment group was associated with decline on any cognitive domain. As in a previous analysis of the entire study cohort, higher A1C values were associated with declines in the psychomotor and mental efficiency domain ($P < 0.01$); however, the previous finding of improved motor speed with lower A1C values was not replicated in this subgroup analysis.

CONCLUSIONS — Despite relatively high rates of severe hypoglycemia, cognitive function did not decline over an extended period of time in the youngest cohort of patients with type 1 diabetes.

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From the [1]Joslin Diabetes Center/Harvard Medical School, Boston, Massachusetts; the [2]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; the [3]Biostatistics Center, George Washington University, Rockville, Maryland; [4]Case Western Reserve University, Cleveland, Ohio; the [5]University of Iowa College of Medicine, Iowa City, Iowa; the [6]Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania; the [7]University of Western Ontario Schulich School of Medicine, London, Ontario, Canada; and the [8]Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

Corresponding author: Gail Musen, gail.musen@joslin.harvard.edu.

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†Deceased.

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Results from the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive diabetes therapy leading to improved glycemic control significantly reduced the risk of microvascular, macrovascular, and neuropathic complications (1). Evaluation of the entire patient group at the end of the trial (2,3) and again after 12 years of additional follow-up with identical comprehensive test batteries revealed that neither intensive diabetes therapy nor history of severe hypoglycemia, which was increased threefold with intensive therapy, was associated with declines in cognitive functioning. There was a modest benefit of improved glycemic control on two cognitive domains: psychomotor and mental efficiency and motor speed (4).

Although severe hypoglycemia did not appear to pose any threat to long-term cognitive functioning in the overall DCCT cohort, it is unclear whether episodes of severe hypoglycemia during childhood or adolescence would increase the risk of cognitive decline in those subjects who entered the DCCT between 13 and 19 years of age. Because of rapid developmental changes in the central nervous system during childhood and adolescence (5,6), younger brains may be more susceptible to insults produced by neuroglycopenia (7). For example, glucose metabolic rates are not comparable with those of adults until late adolescence (6). Indeed, age at time of exposure to metabolic variations of type 1 diabetes could affect their impact on brain functioning and cognitive performance. In addition, there has been debate in the literature as to whether those in whom type 1 diabetes is diagnosed in early childhood (8) show greater cognitive deficits compared with those patients whose diabetes is diagnosed later (9). It has been shown that children and adults with diabetes diagnosed before 7 years of age show mental and motor slowing (10), visuospatial deficits (11), and attentional and executive dysfunction (12). Although it has been suggested that episodes of severe hypo-

glycemia at an early age may be the impetus for these cognitive deficits (11,13), it is also possible that chronic hyperglycemia during childhood makes the brain more vulnerable to subsequent brain injury (14). In the current study we addressed whether hypoglycemic episodes and/or persistent hyperglycemia during adolescence has negative consequences for later cognitive performance in DCCT patients who were between 13 and 19 years of age on entry in the DCCT.

We addressed whether cognitive decline was associated with *1*) assignment to intensive versus conventional therapy for patients who were adolescents during the DCCT, *2*) a history of severe hypoglycemia resulting in coma or seizure, and *3*) the level of long-term glycemic control, as measured by A1C values.

RESEARCH DESIGN AND METHODS

— Between 1983 and 1989, 1,441 subjects with type 1 diabetes were enrolled in the DCCT. A total of 249 subjects were recruited as adolescents aged 13–19 years: 32% were 13–14 years old, 37% were 15–16 years old, and 31% were 17–19 years old. All adolescents had to be at least Tanner stage II in pubertal development, which is the stage at which the first signs of puberty are visible on physical examination. We chose age 19 as the upper age limit, rather than age 18 as used in other studies on the DCCT cohort (15,16), because the sample size was considerably larger when the age limit was extended to the final year of adolescence. The DCCT consisted of two cohorts. The primary prevention cohort ($n = 149$) had diabetes for 1–5 years, no retinopathy, and urinary albumin excretion <40 mg/24 h. The secondary intervention cohort ($n = 100$) had diabetes for 1–15 years, very mild to moderate nonproliferative retinopathy, and urinary albumin excretion ≤200 mg/24 h at baseline. Approximately half of the adolescent sample ($n = 115$) was randomly assigned to intensive therapy (three or more insulin injections daily or subcutaneous infusion with an external pump, guided by frequent self-monitoring of blood glucose) with preprandial blood glucose level targets between 3.9 and 6.7 mmol/l, a monthly A1C target within the nondiabetic range (<6.05%), and a goal of avoiding hypoglycemia. The remainder ($n = 134$) was assigned to conventional therapy with one to two daily insulin injections and no numeric blood glucose targets but freedom from symptoms of hyperglycemia and from frequent or severe hypoglycemia as the therapeutic goal. At the end of the DCCT, this cohort of patients had been studied for an average of 7.3 years (range 4–10). Intensive therapy was recommended for all subjects because it had been shown to be highly effective in reducing complications of long-term diabetes. Subjects in the conventional treatment group were given training in aspects of intensive therapy and then returned to their own health care providers. Between April 2004 and May 2006, 175 participants (76% of surviving, eligible participants) were reevaluated with the cognitive test battery; 74 participants who were adolescents at the DCCT baseline did not participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up cognitive testing. Of these, 6 had died and 12 were inactive at the time of testing.

Cognitive test protocol

Cognitive testing, as originally described for the DCCT (2), was performed at each site by personnel who were trained and certified by the DCCT/EDIC Central Neuropsychological Coding Unit. The test protocol is described elsewhere (2,4). Standardized tests were administered in a fixed order. Capillary blood glucose levels were routinely monitored immediately before testing and at its midpoint to rule out hypoglycemia during testing. If a subject was found to have a blood glucose level ≤3.89 mmol/l, testing was stopped and the patient was given a snack; after waiting at least 15 min, testing was resumed when the reading returned to at least 5.0 mmol/l. Tests scoring procedures are described elsewhere (2,4).

Cognitive domains

During the DCCT, 24 test variables were chosen a priori to be of particular diagnostic value when applied to patients with type 1 diabetes, and a standardized (*Z*) score was calculated for each, with the mean ± SD from the baseline assessment of the DCCT cohort used as a reference (2) to provide a unit-free measurement of the relative improvement or deterioration in performance compared with the total group at baseline. Details of the test variables and domains are described elsewhere (4).

Biomedical evaluations and psychiatric symptoms

During EDIC, subjects completed an annual history, physical examination, electrocardiogram, and laboratory testing, including serum creatinine and hemoglobin A1C, using the same methods as during the DCCT (17). Participants reported the presence of sensory symptoms of peripheral neuropathy as part of neuropathy screening (18).

Psychiatric symptomatology was assessed with the Symptom Checklist-90-Revised (SCL-90R), which was administered annually during the DCCT and once in the EDIC in the same year that the cognitive testing was performed (19,20). For this report, the depression scale was used to assess the effects of mood on cognition.

Definition of severe hypoglycemia

During the DCCT, severe hypoglycemia was defined as any event requiring the assistance of another individual, including seizure or coma, with either blood glucose <2.78 mmol/l and/or subsequent reversal of symptoms with oral carbohydrate, glucagon injection, or intravenous glucose (1). For the purposes of this article, severe hypoglycemic events are limited to those leading to coma and/or seizure because these episodes are the most likely to have an impact on cognition and are most precisely defined. At quarterly visits, study coordinators asked about the occurrence of hypoglycemia since the last visit, and all such events were reported to the Data Coordinating Center as soon as possible after their occurrence. During the EDIC, the severe hypoglycemic events that occurred in the 3 months before the annual visit were documented on the annual history form, and further details surrounding these events were recorded.

Statistical analyses

Demographic and clinical characteristics were compared with the use of Wilcoxon's rank-sum test to evaluate the differences between the treatment groups for ordinal and numeric variables (21). The contingency χ^2 test was used for categorical variables; when the sample size was small, Fisher's exact test was used (21). All treatment group comparisons were based on intention to treat.

Separate analysis of covariance models were used to assess the effects of treatment group (intensive or conventional), mean A1C values stratified by tertiles (<7.9, 7.9–9.5%, and >9.5%), and frequency of severe hypoglycemia (0, 1–5, and >5 reported events) on the standardized quantitative score for each of the eight cognitive domains. Each model ad-

justed for baseline age, sex, education, length of follow-up, visual acuity, self-reported sensory loss attributable to peripheral neuropathy, and the number of interval cognitive tests taken (to control for practice effects). Results are presented as the average increase or decrease in the standardized score from the DCCT baseline within or between groups or as the per unit change in a quantitative covariate. Nominally significant results ($P < 0.01$) are cited.

Analyses were repeated to determine whether cognitive performance was associated with *1*) current mood state measured by the SCL-90R depression scores (scores ≥63 are suggestive of a possible depressive disorder), 2) the timing of severe hypoglycemia, and 3) diabetic ketoacidosis (DKA) during the DCCT.

RESULTS — Table 1 presents the characteristics of the patients at the DCCT baseline and at the EDIC year-12 follow-up. There were no statistically significant between-group differences at the DCCT baseline. The characteristics presented in Table 1 were also compared between patients who continued participation in the EDIC cognitive follow-up and those subjects who were still actively participating in other EDIC evaluations but did not participate in the EDIC cognitive evaluation. The only statistically significant difference was severe nonproliferative diabetic retinopathy at EDIC year 12 (17% participants and 42% nonparticipants). Of the patients who did not participate in the EDIC cognitive follow-up, 45% were assigned to intensive treatment. Furthermore, 16 of 38 had severe nonproliferative diabetic retinopathy, and 12 of 41 had peripheral neuropathy at EDIC year 12. No data on these variables were available for the remaining nonparticipants.

Table 1—*Characteristics of participants who were adolescents at entry into the DCCT*

	DCCT baseline (1983–1989)		EDIC year 12 (2005)	
	Intensive	Conventional	Intensive	Conventional
n	82	93	82	93
Sex (% female)	50	62	50	62
Race (% white)	99	92	99	92
Age (years)	16 ± 2	16 ± 2	36 ± 3	35 ± 3
College graduate (%)	0	0	37	42
Marital status (%)				
Never married	100	99	21	19
Married/remarried	0	1	69	68
Separated/divorced/widowed	0	0	10	13
Occupation (%)				
Professional/technical	1	0	53	41
Unemployed/retired	0	0	2	9
Severe nonproliferative diabetic retinopathy (%)	0	0	11	23
Duration (years)	5 ± 3	5 ± 4	25 ± 4	24 ± 4
A1C†	9.5 ± 1.7	9.4 ± 1.9	7.8 ± 1.5	7.9 ± 1.6
Visual acuity (%)‡			6	4
Peripheral neuropathy (%)§	2	1	17	33
Blood pressure				
Systolic (mmHg)	112 ± 10	109 ± 11	117 ± 13	115 ± 13
Diastolic (mmHg)	71 ± 9	70 ± 9	74 ± 9	75 ± 9
Treated hypertension‖			19	30
Lipids				
Total cholesterol	166 ± 32	165 ± 31	179 ± 34	185 ± 37
LDL cholesterol	102 ± 30	101 ± 28	109 ± 28	113 ± 30
Lipid-lowering medication‖			19	17
Current cigarette smoker (%)	9	11	15	18
Symptom Check List-90R				
Mean depression *T* score	45 ± 10	47 ± 11	49 ± 10	49 ± 12
Verbal IQ¶	110 ± 12	108 ± 12		
Full-scale IQ¶	111 ± 11	110 ± 12		

Data are means ± SD. †DCCT baseline value is the eligibility value. ‡At DCCT baseline, all patients had visual acuity of 20/32 or better. In EDIC, a Snellen value of 20/40 or worse in at least one eye was recorded. §The DCCT baseline definition is pain or numbness in hands only, taken from the Neurological History and Examination form. The EDIC definition is pain or numbness in hands or feet, taken from the Annual Medical History and Examination form. ‖Data were not collected in DCCT. ¶Data were not collected in EDIC. Mean value is 100, with SD of 15. The Wechsler Adult Intelligence Scale was administered for patients aged ≥16 years (58% intensive and 55% conventional), whereas the Wechsler Intelligence Scale for Children was given for participants aged <16 years (43% intensive and 45% conventional).

At EDIC year 12, the age of participants ranged from 29 to 41 years (mean ± SD 35.2 ± 2.5 years). Of the participants, 40% reported having completed a college degree (37% intensive and 42% conventional), and almost 50% reported a professional or technical occupation (53% intensive and 41% conventional). At EDIC year 12, differences between the two treatment groups approached significance for the presence of peripheral neuropathy and severe nonproliferative diabetic retinopathy ($P < 0.05$).

Over the entire 18-year follow-up, there were a total of 294 reported episodes of coma or seizure. Of these, 200 were reported in 51 intensive treatment group subjects and 94 were reported in 36 conventional treatment group subjects (Table 2).

A separate analysis conducted between the primary and secondary patient cohorts differing in terms of diabetes duration and complications revealed no effect of diabetes duration between these two groups. Table 3 summarizes the raw scores for each cognitive test, stratified by treatment group. Figure 1 shows cognitive test results for each domain by original treatment group (Fig. 1*A*), cumulative number of severe hypoglycemic events (0, 1–5, and >5 episodes) (Fig. 1*B*), and metabolic control (tertiles of mean A1C values) (Fig. 1*C*). Neither original treatment assignment nor cumulative number of hypoglycemic events influenced performance in any cognitive domain. Age did not significantly affect cognition. Performance in both sexes improved over time, and this effect was more pronounced in male participants ($P < 0.01$). Higher values of A1C were associated with modest declines in psychomotor and mental efficiency ($P < 0.01$). Degree of self-reported symptoms of depression at year 12, as indexed by the SCL-90R (median *T* score 46.0; scores ≥63 reflect possible depressive disorder), was

Table 2—*Severe hypoglycemic events (coma/seizure) among participants who were adolescents at entry into the DCCT*

	DCCT		EDIC		Total follow-up	
	Intensive	Conventional	Intensive	Conventional	Intensive	Conventional
n	82	93	82	93	82	93
Events						
0	35	72	61	67	31	57
1–5	39	17	20	26	40	31
>5*	8	4	1	0	11	5
Total patients with 1+ event	47	21	21	26	51	36
Total events	155	53	45	41	200	94

All DCCT hypoglycemic events were documented. EDIC hypoglycemic events were documented in the 3-month period before the annual visit. *Number of events ranged from 1 to 18 in the intensive group and 1 to 11 in the conventional group.

not associated with poorer performance on any of the eight domains. Analyses were repeated using the broader definition of hypoglycemia, which includes episodes in which the patient has incapacity sufficient to require assistance. The results with the broad definition were similar to those obtained using the narrow definition (i.e., restricted to seizure or coma).

The timing of severe hypoglycemic events did not affect performance on any of the eight cognitive domains. We found that 47 patients reported their first episode of coma or seizure during adoles-

Table 3—*Raw cognitive test scores*

	DCCT baseline (1983–1989)		EDIC year 12 (2005)	
	Intensive	Conventional	Intensive	Conventional
n	82	93	82	93
Problem solving				
Similarities*	12.2 ± 2.8	12.1 ± 2.5	13.8 ± 2.2	13.1 ± 2.4
Category test (no. errors)†	30.7 ± 18.2	32.3 ± 22.9	15.0 ± 10.8	14.9 ± 12.9
Learning				
Symbol-digit learning (no. correct)	24.5 ± 4.3	24.5 ± 4.5	25.7 ± 2.9	24.8 ± 4.4
Tactual performance memory (no. correct)	7.4 ± 1.5	7.3 ± 1.7	8.1 ± 1.2	7.8 ± 1.5
Immediate memory				
Visual reproductions (no. correct)	14.6 ± 1.9	14.5 ± 2.4	15.3 ± 1.5	15.1 ± 1.7
Short-term memory (no. correct)	38.0 ± 9.5	37.5 ± 10.2	42.7 ± 11.0	40.1 ± 11.8
Logical memory (no. correct)	19.7 ± 5.7	19.5 ± 5.4	20.9 ± 8.5	20.0 ± 5.3
Digit symbol (no. correct)	8.4 ± 1.0	8.1 ± 1.4	8.0 ± 1.6	7.9 ± 1.5
Delayed recall				
Visual reproductions (no. correct)	15.5 ± 1.5	15.4 ± 1.7	15.5 ± 1.4	15.3 ± 1.7
Logical memory (no. correct)	15.9 ± 5.2	16.3 ± 5.2	18.4 ± 8.9	17.9 ± 8.0
Spatial information				
Embedded figures (time in s)†	7.4 ± 3.2	7.0 ± 2.6	5.5 ± 2.6	5.3 ± 2.2
Object assembly*	11.5 ± 2.6	12.0 ± 2.8	14.5 ± 2.5	14.2 ± 2.7
Block design*	12.6 ± 2.4	12.1 ± 2.8	14.1 ± 2.4	13.8 ± 2.8
Tactual performance test (time in min) †	10.7 ± 3.8	10.9 ± 3.4	8.6 ± 3.1	9.4 ± 3.0
Attention				
Digit vigilance (time in s)†	398.8 ± 77.9	401.5 ± 91.2	365.2 ± 80.0	386.1 ± 84.6
Digit vigilance (no. errors)†	6.0 ± 5.7	6.4 ± 5.6	5.4 ± 6.1	6.2 ± 6.2
Digit span*	11.1 ± 3.0	11.1 ± 2.7	12.2 ± 2.8	11.8 ± 3.1
Psychomotor and mental efficiency				
Verbal fluency (no. correct)	37.8 ± 9.3	37.4 ± 10.4	48.8 ± 12.7	45.6 ± 13.6
Digit symbol, 90-s total (no. correct)	62.4 ± 13.1	60.2 ± 11.4	67.8 ± 10.5	66.3 ± 9.1
Trail making, part B (time in s)†	51.3 ± 16.6	51.9 ± 16.2	45.6 ± 12.8	48.9 ± 15.1
Grooved peg test, dominant hand (time in s)†	66.4 ± 10.4	66.9 ± 9.4	66.0 ± 11.3	66.9 ± 13.0
Grooved peg test, nondominant hand (time in s)†	71.0 ± 10.7	72.8 ± 12.3	72.0 ± 12.2	74.4 ± 17.8
Motor speed				
Finger tapping, dominant hand (no. taps in 10 s)	46.0 ± 6.9	45.0 ± 6.4	52.1 ± 7.1	50.6 ± 7.1
Finger tapping, nondominant hand (no. taps in 10 s)	43.0 ± 6.4	41.7 ± 5.8	46.9 ± 5.9	44.5 ± 7.1

Data are means ±SD. *Scaled scores. †Higher scores indicate poorer performance.

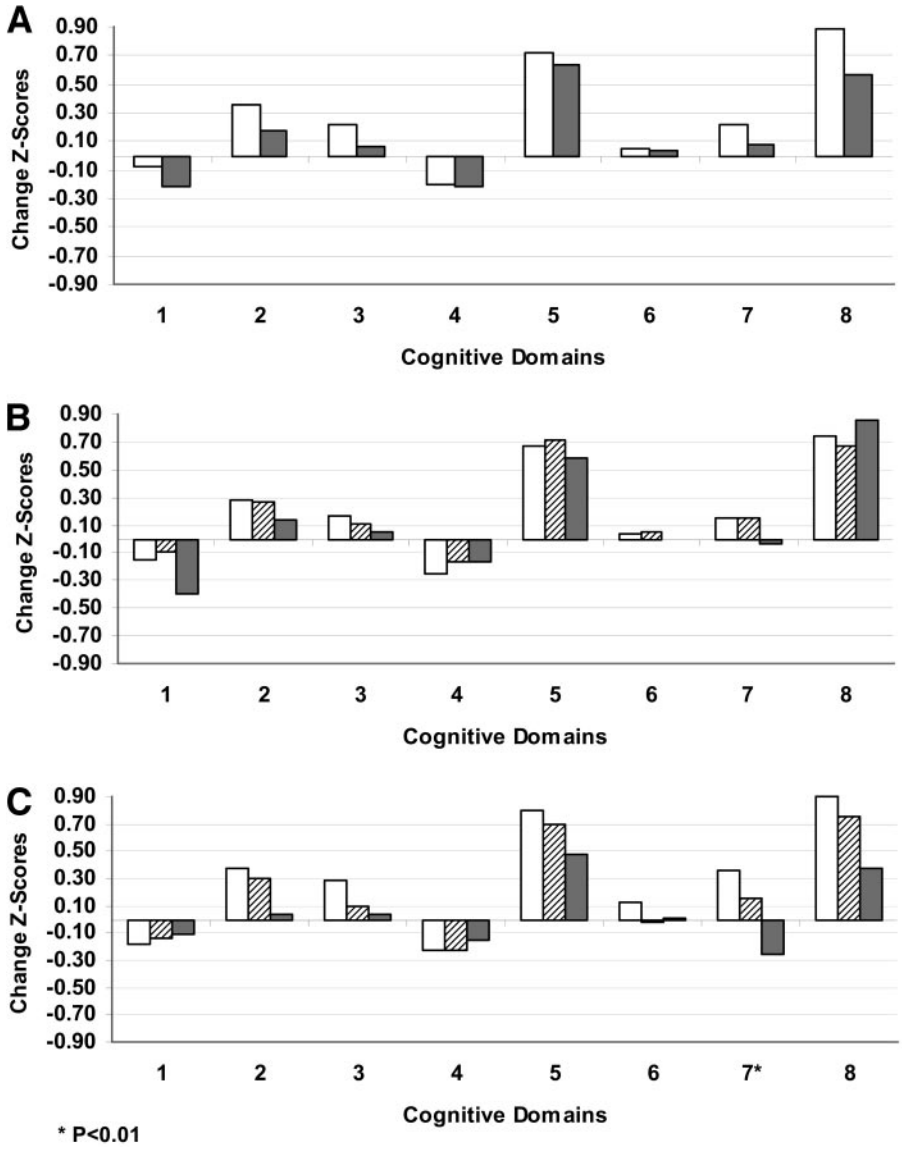

Figure 1—*Changes in cognitive domains between DCCT baseline cognitive testing and follow-up testing (mean of 18 years after baseline) based on change in Z scores for intensive (□) vs. conventional (■) treatment groups* (A)*, frequency of severe hypoglycemia (coma or seizure) episodes (no episodes □, 1–5 espisodes ▨, or >5 episodes ■)* (B)*, and tertiles of mean A1C (<7.9% □, ≤7.9% ▨, or <9.5% ■)* (C)*. 1, Problem solving; 2, learning; 3, immediate memory; 4, delayed recall; 5, spatial information; 6, attention; 7, psychomotor and mental efficiency; and 8, motor speed. ANCOVA models were used with adjustments for baseline age, sex, years of education, length of follow-up, visual acuity, self-reported sensory loss due to peripheral neuropathy, and the number of interval cognitive tests taken. Neither treatment group nor cumulative number of hypoglycemic episodes influenced performance in any cognitive domain. Higher values of A1C were associated with modest declines in psychomotor and mental efficiency ($P < 0.01$).*

cence (ages 13–19) and 43 patients reported having lost consciousness between one and five times before their DCCT baseline evaluation. Further, there was no synergistic effect of hypoglycemia and hyperglycemia on cognition. Patients who experienced DKA ($n = 26$) during the DCCT (ages 13–19 years) declined in cognitive performance on the learning domain, whereas the patients without DKA improved. Further, patients with DKA episodes during the DCCT improved less on the spatial information domain than patients with no DKA events (data not shown).

CONCLUSIONS — Our previous report on the entire DCCT/EDIC cohort showed no detrimental effects of intensive treatment or severe hypoglycemic episodes on cognitive performance (4). However, because of the potential vulnerability of the developing brain (14), we evaluated whether intensive treatment during adolescent years posed threats to long-term cognitive functioning. Severe hypoglycemic episodes during childhood are a major concern, especially given the findings that cognitive deficits may be more common in those in whom type 1 diabetes is diagnosed during childhood (9,12,22). Moreover, children may be more sensitive than adults to even modestly lower glucose levels, with cognitive deterioration at ~3.3 versus 2.5 mmol/l in adults (23).

Our results closely resemble those previously reported for the entire cohort (4). Intensive treatment is not associated with risk for long-term cognitive dysfunction, even in the subset of patients who entered the DCCT during adolescence. As with the findings from the entire cohort, we found that higher A1C values were associated with poorer performance on measures of psychomotor and mental efficiency, which require the integration of motor and cognitive processes. This finding further highlights the benefits of intensive glycemic control. Higher A1C values were also associated with somewhat slower performance on a simple measure of motor speed (Fig. 1), but, unlike our earlier results with the entire cohort, that effect failed to reach statistical significance in this cohort, possibly due to smaller sample size. Although we collected data on retinopathy, which are associated with higher A1C levels, the effect that this complication has on cognitive ability is beyond the scope of the article and will be addressed separately.

Despite no discernible ill effects on cognition as a result of severe hypoglycemia, brain abnormalities due to serious hypoglycemia have been observed in other studies. For example, children with a history of severe hypoglycemia have shown some abnormalities in brain structure and function (22). Slow-wave electroencephalographic activity is increased in this patient population, especially in the frontal regions (24), which govern executive function and attention. Finally, recent evidence has suggested that severe hypoglycemia in children alters gray matter density (22), analogous to what has been reported in young adults with type 1 diabetes (25). There is not always a direct relationship between brain changes and behavioral effects. Thus, although no notable cognitive deficits were observed, these early brain changes may serve as a marker of future cognitive impairments (25).

Although our conclusion from this study is that severe hypoglycemic episodes

have no long-term effect on cognition, even when experienced during adolescence, several study limitations need to be considered. First, we included patients between the ages of 13 and 19 years; therefore, we cannot determine whether diabetes or hypoglycemia during early childhood is associated with cognitive deficits later in life. Accordingly, we have limited information on the effects of diabetes on the very young brain. Second, the results must be generalized cautiously not only because the sample size of our cohort is relatively small but also because of the careful selection criteria applied to subjects recruited into the DCCT. Third, our study imposed restrictions on the number and severity of DKA and hypoglycemic episodes that patients could experience during the several years before the DCCT. These exclusionary factors restrict our ability to comment on whether long-term cognition is further affected in patients who experienced these particularly serious metabolic consequences of diabetes.

In summary, our study indicates that with regard to long-term cognitive function, intensive treatment is safe for patients who had the diagnosis of diabetes as children, despite the increased threat of severe hypoglycemic episodes. Nevertheless, we need to remain cognizant of the dangers of acute hypoglycemia, which can lead to comas, accidents, injuries, death, family stress, loss of school or work time, and loss of commitment to the goals of intensive treatment. Thus, continued research is needed to develop new therapies and technologies that will minimize or eliminate this major obstacle to achievement of optimal control of type 1 diabetes.

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